Kidney International, Vol. 39 (1991), pp. 787–792

HISTORICAL ARCHIVE
EDITED BY CARL W. GOTTSCHALK

From Bright's disease to modern nephrology: Pierre Rayer's innovative method of clinical investigation

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From Bright's disease to modern nephrology: Pierre Rayer's innovative method of clinical investigation. Pierre Rayer, in a day of purely descriptive medicine, devised a method for the scientific study of diseases affecting the kidney and urinary tract. He first assembled vivid illustrations of a wide range of disorders of the kidney found in specimens obtained at autopsy. The resulting *Atlas* won him widespread praise and is still often cited. His *Treatise* (*Traité des Maladies des Reins et des Altérations de la Sécrétion Urinaire*), in which he integrated data from pathological anatomy with urinary biology and clinical manifestations, was ahead of its time. Hence it was poorly understood and, like the work of many other innovators, was largely ignored. Nevertheless, his 2100 page *Traité* which begins with a description of his innovative and highly disciplined method of study, most unusual at this time, is by no means lacking in interest for today's nephrologists. Rayer's was a landmark contribution, affording, as it did, a comprehensive approach to the clinical problems of nephrology a century before the diseases themselves could be understood. Could a contemporary of Rayer tell that he was an inventor of scientific methodology before the proof of his rigorous demonstrations was carried out? That has been the achievement of clinical nephrology in the past forty years . . . one century later.

In 1837 Pierre Rayer (1793–1867) published an *Atlas* [1] as the initial component of his three volume *Treatise on Diseases of the Kidney* which appeared from 1839 to 1841 [2]. The *Atlas* illustrated lesions throughout the renal excretory tract, most of which had never before been described. The book met with international acclaim and has remained a classic to this day. Rayer's subsequently published *Treatise*, entirely unfamiliar to his contemporaries, was initially greeted with amazement but was soon forgotten. Rayer's approach, which anticipated modern clinical science by bringing biology into the clinic, was too innovative to be understood at the time.

Rayer forcefully states in 250 pages his novel objective in the *Preface* which then leads into a long *Prolegomena*, an obsolete term applied to a preliminary chapter that pulls together the basic requirements for understanding the remainder of the book. Rayer defined both old and new material in the fashion of an encyclopedia, analyzing each item critically before incorporating it into a logical scheme for sorting out the data and matching them in a scientifically valid fashion to each morbid condition. The present paper focuses on the *Preface* and *Prolegomena*.

Received for publication June 8, 1990
and in revised form October 26, 1990
Accepted for publication October 26, 1990

Preface, a manifesto

Rayer, as a well known pathologist, was fully aware of the weakness of morphological information at the time. Nevertheless he could not have conceived his *Treatise* without the basic, high quality anatomical data which his own meticulous pathological investigations afforded. Autopsies were rarely done in his day, as was evident from the debates in the House of Commons in 1832 from which rules to facilitate anatomical verification emerged [3]. Moreover, the kidneys had scarcely been examined. Hence, as Rayer commented: "It is widely believed that lesions of these organs [the kidneys] are rare." (p. VI) He advocated the study of all pathological findings, even those at a distance from the kidney because (p. XI), as he added: "There are hardly any diseases confined to a single locality . . . It is that conviction that dominates all of my work."

Careful study of the urine was another of Rayer's concerns. "In truth," he wrote, "to ignore alterations in the composition of the urine is to close the door to useful observations and thus to lose the chance of establishing proper diagnosis and treatment (p. V). "By studying individually all aspects of urinary secretion, including examination of the urine in all renal diseases, in other disorders of the urinary tract, disorders of other organ systems and systemic diseases as well, I have been able through comparative study, to attach diagnostic and prognostic significance to each of the various findings (p. VII)." Thus Rayer was able, using verified data, to distinguish among a host of renal affections without intellectual bias.

The prolegomenas

General pathology of the kidneys

Rayer worked only with gross specimens. Not until Gabriel Valentin's (1810–1883) poorly documented paper published in 1837 was there any report of microscopy of the kidney [4]. Rayer's prolegomena contained 57 pages of weights and measurements of normal and pathological renal tissue. He described the findings in sketchy fashion but nevertheless quantified the data, which is in keeping with his concern with statistics which dating back to 1822 when he was studying an epidemic of "Suette Miliaire" [5], miliary fever due to partial occlusion of the sweat glands.

In his *Atlas* and the *Treatise*, known and previously recognized lesions were classified in tabular form together with associated abnormalities in the kidney along the renal excretory pathway, or elsewhere.

Rayer's classification went beyond the descriptions of Bright's disease by linking the renal abnormalities to clinical manifestations and anatomical findings, urinary or otherwise.

Carefully evaluating the significance of such previously neglected urinary abnormalities and relating them without bias to the pathological manifestations in the various disorders yielded, rather than a unified pattern, a set of different patterns relating in one way or another to the kidney. "Since these disorders involve the same organ and the same function," he wrote, "they are doubtless related in some way; but careful study of the circumstances of their development, their onset and course leads to the conviction that earnest efforts to encompass them in a generalized formulation would be fruitless." (p. 40). This view, reflecting as it does a physiopathologic attitude of probing for specific signs where differences have more weight than do frequently inaccurate groupings based on analogy, brings to mind the approach of Claude Bernard (1811–1878), who was Rayer's devoted pupil. Rayer's way of approaching the study of the urine, outlined in the next section, gives further evidence of the filial relationship in their ways of thinking.

General consideration of the urine

In the *Preface* Rayer states boldly: "Kidney disorders and alterations of the urine are tightly linked together; study of one requires study of the other. To the degree that urinary findings are ignored, the understanding of kidney diseases is obscured." (p. V). Although many of the data Rayer provides are imprecise, his physical and chemical methods and his microscopic interpretations endow this section with originality and scientific rigor. They deserve attention.

Physical methods. Rayer makes no innovation here but applies his techniques with scrupulous care. To measure *density* he used the simple aerometer of Baumé in preference to the clinically too sophisticated weight/volume ratio, because he had established a table of equivalence of the two methods by making multiple comparisons in various physiological and pathological conditions. Thereby, as he acknowledged, he confirmed the work of Charles Chossat (1796–1875) in Geneva [6] and Thomas Thomson (1773–1852) in Glascow. Although Rayer did not add much to the contributions of the schools of Richard Bright (1789–1858) or Robert Christison of Edinburgh (1797–1882), he did make one intriguing original observation. Rayer noted, although without providing the quantitative data, that the density of "healthy urine" is higher than that of "chronic albuminous nephritis" where "the presence of albumin is more than compensated for by the marked reduction of urea as well as certain salts" (p. 73).

Urinary acidity and alkalinity. To measure titratable acid, Rayer neutralized the urine with a very dilute solution of ammonia, similar to what we do today with NaOH. Again, there was no innovation but he did note that uric acid stones "gravelle urique," were often associated with highly acid urine and, moreover, that the condition could be effectively corrected, although for only a few hours, by taking alkali. Therefore Rayer recommended that alkali be administered at regular intervals around the clock. He further recognized the link between pyuria and alkaline urine.

Chemical techniques. Rayer wanted to construct a well supported clinicochemical semiology.

The lack of a satisfactory method for measuring *urea concentration* forced him to resort to techniques that were semiquantitative at best. They did enable him, however, to recognize that the presence of pus or albumin in the urine does not interfere with the measurement of urea. Moreover, he noted that production of ammonia from urinary urea induced alkalinization (p. 85), thus causing the urea to disappear. Even without accurate measurement Rayer was able to refute William Prout's (1785–1850) postulation of a "ureic diabetes" similar to diabetes mellitus [7] with the comment: . . . "the cases in which it (urea) is reduced are very common, perhaps due not so much to the diseases themselves as to the attendant fasting and consequent debility." Thus his good clinical insight compensated for the deficiencies of chemistry and physiology that prevailed in his day.

"Normal urine," he wrote: "does not contain albumin but one can extract albumin in various quantities in several diseases (notably in albuminous nephritis)." Thus Rayer begins his chapter on *albuminuria* (p. 134).

To provide a quantitative measure of albumin Rayer tested several methods, rejecting those that caused precipitation of substances other than albumin. He settled on heat coagulation that, with acidification, eliminated urinary opacities due to other substances.

Rayer was not the discoverer of albuminuria but, as a scientifically minded physician, he studied it thoroughly. Among 70 sick children he found urinary albumin in only the three who were edematous (Vol 2, p. 610). He also noted that albuminuria was present from time to time in several acute illnesses. Besides such confirmations of earlier findings Rayer drew new conclusions from the association of albuminuria with other disorders, mainly urinary. This led him to offer 22 premises, most of which turned out to be entirely correct. He had validated several of the associations with microscopic study of the urine, a technique for which Rayer became a zealous promoter. As already noted, microscopic examination of tissue slices had not yet come into use.

Microscopic examination of the urine. Microscopy was perfected during the decade of the 1820's, thanks to the extraordinary skill of Charles Louis Chevalier (1804–1859), who managed to create an achromatic lens small enough for use in a microscope, thereby achieving control of iridescence [8]. The development of this important innovation was based on the discovery of the achromatic lens by Peter Dolland in England (1706–1761) and its perfection by Joseph Von Fraunhofer (1787–1826) in Bavaria. This major instrument of progress for biology was seized upon by Rayer who saw in the microscopic examination of the urinary sediment the first step toward the study of the pathology of the kidney in vivo. By 1835, at least, Rayer had installed a microscope on the ward, close to the patients, at l'Hôpital de la Charité.

After concentrating the urine, by adding acids or alkalies and studying in hot or cold solutions the form of the crystals that appeared, Rayer was able to identify the *minerals deposited.* Thus he adapted the microscope to the study of microcrystallography, improving the classical magnifying glass technique of

Abbé Haüy (1743–1822) and William H. Wollaston (1766–1826). It proved very useful in evaluating the risk of impending renal calculi. Eventually he even discovered crystals of quinine sulfate in the urine of a treated patient as illustrated on one of the plates in volume one, a first in clinical pharmacology.

By focusing on non-mineral deposits, Rayer opened an entirely new field of investigation. He was able to identify microscopically blood, pus, mucus, epithelial cells, sperm, chyle or fat globules. Moreover, microscopy sometimes disclosed these substances in a clear urine. Adding them to normal urine enabled him to test the sensitivity of the method. Rayer was thus able to detect microscopic hematuria coupled with albuminuria and thereby identify "albuminous nephritis," and persistent microhematuria after an acute bout as well as microscopic pyuria of pyelonephritis and pyelitis.

Rayer was thus in a position to make a clinical differentiation between the two major types of nephropathy: "albuminous nephritis," inflammatory but not suppurative, the glomerulonephritis of today, corresponding to traditional chronic Bright's disease, including the acute type, also characterized by albuminuria with microscopic hematuria. The second is the suppurative nephritis with pyuria, known before Bright's important work at Guy's Hospital, but later forgotten. Rayer divided the suppurative nephritides into two groups, a simple form, apparently corresponding to hematogenous renal infection and pyelonephritis due to ascending infection in urological disorders. He was able to make the discrimination between the two forms of renal suppuration by virtue of his meticulous examination at autopsy of the entire urinary tract and all other organs as well.

Rayer's clear delineation and documentation of the two major forms of nephritis with clinical, anatomical and, for the first time, biological inquiry fell on deaf ears. Not even the smallest revision of the teachings of Bright was accepted. Bright's disease remained a single category. Not until the technique of kidney biopsy became available to demonstrate the diversity of lesions capable of producing terminal nephritis was there a general willingness to make an etiological and/or pathologic subdivision of Bright's disease. A presentation at the 1961 conference sponsored by the CIBA Foundation, "The fine structure of the glomerulus in Bright's disease," at last settled the issue [9].

Thanks to its innovative method of inquiry, at once pathological and biological, Rayer's *Traité* made a major contribution to nosology. The cellular theory of Matthias J. Schleiden (1804–1881) and Theodor Schwann (1810–1882) was just emerging. Rayer, however, could have spoken about cells instead of "globules of pus." Indeed, Arnold Rich [10] had dated the cellular hypothesis as early as 1824, stemming from the work of René Dutrochet (1776–1847) [11]. Nevertheless, the credit belongs to Rayer for establishing the suppurative nephritides, acute and chronic, as clinical entities. His work preceded the Pasteur revolution by 30 years.

Historical perspective

Rayer divided the history of nephrological knowledge into three parts: the study of the nature of the urine itself, its chemistry, and the concept of clinico-chemical correlation which he was proud to have inaugurated and fixed his seal upon. The pages of the *Traité* devoted to the first two steps contain a gold mine of references for historians. In the following pages he credits Cruickshank for his contribution to the work of Rollo [12], then Nysten [13] followed by Prout [7], Bostock [14] and finally Rees [15] whose studies, published in 1836, were characteristic of the school of Richard Bright. By placing the historical background after the presentation of his own work Rayer seemed to be making a case that he had created a methodological breakthrough in technique and logic and had made a clear departure from the achievements of his predecessors.

The relationship of urinary abnormalities to disorders of blood and other fluids

In this section Rayer takes a look at the future without speculation but with an expressed hope: "By re-emphasizing certain well established facts, I hope to have put to rest the prejudices that vitalist physicians have entertained against the type of research that I have described."

Rayer revived the notion earlier put forward by Rouelle le Cadet (1718–1779) in 1773 [16], elaborated in 1799 by Antoine Fourcroy (1755–1809) and Nicolas Vauquelin (1763–1829) [17], on the role of the kidney in regulating nitrogen metabolism. He focused on two blood disorders. In discussing one of them, the hypoalbuminemia of massive albuminuria, he failed to assign adequate recognition to the school of Bright. The other condition was urea retention, uremia in which he cited the convincing evidence derived from nephrectomized animals by Jean Louis Prevost (1790–1850) and Jean Baptiste Dumas (1800–1884) [18], whose experiments were confirmed by Leopold Gmelin (1788–1853) and J. Tiedmann (1781–1853) [19], and then by R.C. Marchand (1813–1850) [20]. In contrast he expressed no confidence in the chemical assertions of such clinicians as Nysten [13], Christison [21], Bostock [14] and Gregory [22]. Moreover, without excluding urea retention as a possible cause of pathology in man, he reserved judgement pending appropriate chemical evidence, a characteristic submission to the discipline of science.

An important deficiency—physiological correlations

While Rayer well organized his urinary and pathologic data he failed to integrate them with physiology. Although current knowledge of chemistry did not permit reproducible measurement of urinary constituents and that understanding of their metabolic significance was rudimentary at best, Rayer should, nevertheless, have been able to draw physiological inferences from his observations on urinary nitrogen and urea. Their animal and vegetable sources were well known from the work of Fourcroy and Vauquelin [23] and François Magendie (1783–1855) [24]. Although Rayer was unable to obtain an accurate measurement of urea, he could have tried to study the influence of various foods on urinary density. Chossat [16], briefly quoted by Rayer, had been able to gather approximate data on urinary density from animals and even managed to approach the idea of metabolic balance by studying 24 hour urines. Work was clearly leading toward the quantitative study of metabolism, even though the investigator was not aware of the goal.

Water was, of course, pertinent to renal investigations. Illustrious early workers such as Antoine L. Lavoisier (1743–1794) and Armand Seguin (1765–1835) had, by making measurements of expired water and of the body weight of one another,

been able to estimate the contribution of respiration to water balance. The kidney's role in water balance should have been much easier to study. But Rayer neglected it as had Lavoisier.

Rayer's *Traité* antedated the dawn of metabolic physiology. It was not until 25 years after its publication that contributions of Max Pettenkoffer (1818–1901) and Carl Voit (1831–1908) began to sort out the role of the urinary constituents in metabolic balance. With respect to the formation of urine, the *Traité* appeared just before the two contributions that opened the era of modern renal physiology. William Bowmann's (1816–1892) demonstration in 1842 of the glomerulotubular passage and Carl Ludwig's (1816–1895) discovery of glomerular filtration, reported in his thesis in 1843.

Rayer was by no means opposed to physiology, as is evident from his intellectual ties to Claude Bernard and other pupils who were working in that discipline. His unwillingness to make inferences without the evidence at hand may indicate a wise scientific restraint or, perhaps, simply an exaggerated fear of being wrong.

Rayer and the clinical nephrology of his time

The fact that Rayer had introduced Bright's work [26, 27] into France as well as the work of the Edinburgh group led by J.C. Gregory and Robert Christison [21] was attested to in the list of the theses upheld by the Faculté de Médecine in Paris from 1816 to 1842.

From 1816 to 1832 thirty-six theses among a total of 3200 related to the kidney. Of the 30 that are available 23 deal with acute nephritis with unilateral flank pain, apparently indicating infection secondary to renal lithiasis. After 1832 Bright's name appeared prominently in the theses of three of Rayer's pupils: Tissot [28] (1833) who, in a study of edema confirmed the studies from Guy's Hospital; and Désir, [29] whose thesis in 1835 reported a systematic study of the detection and semiological value of albumin. His thesis concluded with an experimental approach in which he added measured amounts of egg white to control his data on the clinical specimens. The third was Bureau [30], whose 1837 thesis on "Albuminous Nephritis" established the fact that pus in the urine identifies pyelitis as distinct from albuminous nephritis. Vigla, the intern with whom Rayer studied pyuria microscopically [31], published his results in 1838 in *L'Expérience*, the journal of Emile Littré (1801–1881), a great friend of Rayer.

Urinary semiology was repeatedly dealt with in theses ranging from 1838 to 1842. After that, when Rayer abandoned the kidney to devote his efforts to the study of those diseases in animals that were transmissible to humans [32], interest in the kidney in Paris faded.

At that time other European investigators were publishing studies on renal disorders that had been carried out in a fashion that differed sharply from the approach of Rayer. Thorough examinations by Bright [27] and Rees [15] of the pathological lesions of chronic Bright's disease included the testing of urines in the old fashioned way. In his monograph (1839) R. Christison expressed surprise at the lack of interest in the kidney in the country of Bright. Christison's interest was focused mainly on the end stages of renal disease. He provided a clinical, biological and anatomical description of exemplary clarity without altogether neglecting spontaneously curable acute forms. He did not slight Rayer's work in any way and even commented that in the future "more than one organic derangement" will be uncovered, but he overlooked the distinction made by Rayer between suppurative and non-suppurative nephritis.

"L'Albuminurie," published in 1838 by J. Martin Solon (1794–1856) continued the existing confusion as it grouped together all of the albuminurias, even the chemically doubtful ones. In 1841, Alfred Becquerel (1814–1862) [35], a pupil of Andral, published a book on the examination of urine in which he, too, hewed close to the techniques of Bright without any new twist. Finally, in 1851 F.T. Frerichs' (1819–1885) monograph appeared, focusing on uremia, Urämische Intoxikation [36]. By that time the chemical properties of blood were no longer so obscure as they had been in Rayer's day. Rayer's work was, therefore, farseeing and unique, not only in his own country but throughout Europe.

The only translations of Rayer's *Traité* were in German by S. Landmann[1] and by G. Krupp [37]. Never republished in France, it was soon forgotten by everyone except Lécorché and Talamon [38], Ménétrier [39], then Ackerknecht [40], and finally E. Ritz [41] and S. Cameron [42], who ascribed to Rayer the credit he deserved.

Who was Pierre François Rayer?

Born in 1793 in Normandy, Rayer studied in Paris where he won top academic distinction in two subjects at opposite poles of the scientific spectrum, chemistry and anatomy. Such intellectual breadth characterized his entire life.

In addition to his *Maladies des Reins* Rayer produced other medical work of high merit. In his 1818 thesis on *The History of Pathological Anatomy* he championed comparative pathology and proclaimed the union of pathology and chemistry. His study in 1822 of the epidemic of Suette Miliaire (miliary fever) north of Paris was rich in epidemiological and statistical data [15]. In 1837 he succeeded in transmitting glanders from a patient to horses. Later, in 1850, he performed a microscopic study with C.J. Davaine (1812–1882) of the blood of sheep stricken with malignant anthrax, and saw little rods that 30 years later would be identified as anthrax bacteria.

In 1826 he published a *Traité des Maladies de la Peau* (Treatise on Skin Diseases) in three volumes and an *Atlas* with 400 illustrations. He organized that classical work in the manner of the Hungarian, Joseph Plenck of Tyrnau (1732–1807), whose classifications of cutaneous lesions were inspired by Linneus (1707–1778) and of Robert Willan (1753–1812), who further refined their categorization. Rayer brought to bear clinical analyses and gross anatomical distinctions, rejecting etiology as too uncertain to serve as a basis for classification [43]. Rayer's

[1] S. Landmann did not, strictly speaking, translate the *Traité*. He, in fact, made a clever use of multiple subtitles to bring out in a clearly written, 600 page compendium the specific changes and additions brought by Rayer's work to the discoveries of Bright's and Christinson's groups. His excellent "Vorwort" offers a precise appraisal of the pioneering method used by Rayer to broaden the clinical, pathological and biological approaches of renal diseases. Landmann is probably the physician who best understood at the time the advantages of Rayer's method. Who was he? An academic physician? A scholar? Or just a distinguished practitioner in Anspach, Bavaria where he lived? We do not know. However, his book is well worth reading. It brings to light an aspect of the intellectual life in Europe and of the interest for nephrology in the middle of the 19th century.

method led by a macroscopic pathological approach to dermatology presaged his biological approach to nephrology. Finally his *Traité* was republished and translated into several languages, including Arabic, attesting to its success—which was ultimately greater in Germany and England than in France [44].

Rayer, as head of his own school of research, was "a fisher of men" and was "distinguished by the achievements of his pupils as well as by his own work" according to Philippe Ricord (1800–1889) an American who became the most famous venereologist in Paris. Rayer's impressive list of pupils included Claude Bernard, Emile Littré, Charles Robin, Jean Martin Charcot, Marcellin Berthelot, Charles Brown Sequard, Charles Bouchard, etc. He supported them all with his counsel, his interest, his affection, and at times by his money. Founder and first president of the Société de Biologie in 1849, he served with the other officers, Claude Bernard and Charles Robin. Under his leadership the Société de Biologie became the forum where for decades were presented many major discoveries in medicine and biology.[2]

Although Rayer was physician to King Louis Philippe and the Emperor Napoleon III, as well as other powerful figures, he never hid his liberal convictions. His views did not protect him from other liberals, however; when he became dean of the Faculté de Médecine in 1862, Ernest Renan (1823–1890) dubbed him "the dean created by a coup d'état at the Faculté de Médecine." The students called him a "creature of the empire" and forced his resignation in 1864 in the fashion of an ancient tradition of the Latin Quarter. The students drove him away by their rowdy behavior, preventing him from giving his course in comparative pathology. It was a painful defeat for Rayer, a liberal rationalist as he had declared himself to be in his 1818 thesis about "the universality of the science of organized creatures, animals and vegetable." His ideas were shared by Dutrochet [10, 11] and Claude Bernard, who in 1878 published "Leçons sur les Phénomènes de la Vie Communs aux Animaux et Végétaux." As Dean of the Faculté de Médecine, an organizer despite the hostile climate, he sent S. Jaccoud (1830–1913) to Germany to study the organization of the German hospital laboratories before modifying and expanding those in Paris, a task he was able to accomplish only in part due to his short stay.

Rayer died in Paris in 1867. An impressive number of world renowned figures, noble and otherwise, took part in his funeral, thus attesting to his social success [45]. Among the pallbearers, all prominent persons, were Ricord and the Duke of Fitz-James. His fortune must have been considerable. He was certainly never in financial need. As a physician, attentive to everyone and generous to a fault to the poor, he founded the first support group for practitioners who, for one reason or another, were destitute.

Rayer and Gabriel Andral (1797–1876), his friend, followed the same path [40]. As dedicated anatomo-pathologists of high quality, they were fully committed but not enslaved by their discipline. Driven as they were by scientific doubt, and sensitive to the weakness of existing techniques, but mindful of the productive paths to follow, they contributed broadly to an unsettled biology.

The memory of Rayer is surely buried in the solidified lava of the ancient history of medicine. His legacy was his method, the first fruits of modern clinical science. Nephrology was its first beneficiary. Can she forget him?

[2] Although beyond the scope of this paper, the links uniting Rayer, Claude Bernard and the Société de Biologie deserve a special mention. Rayer singled out the young Bernard as a student and provided him with a position of "préparateur" in François Magendie's laboratory (1783–1855). Subsequently, under Rayer's leadership Bernard launched, among others, two successful studies. One was the dissection of the nerves in cases of facial paralysis with or without loss of the sense of taste: the sensitive deficit could be related to the involvement of the corda tympani. The second was a "chemical" autopsy of a diabetic detecting an accumulation of sugar in some organs and not in others; it is one of the first steps of Bernard's study on glucose metabolism. This breakthrough was published by Rayer and Bernard on one and a half pages of the Comptes Rendus de la Société de Biologie 1849 I, pp. 80–81. The Société de Biologie had been recently founded by physicians influenced by the positivist Auguste Comte (1798–1857) to whom Rayer had introduced Bernard. Charles Robin (1821–1885), vice president of the Société together with Bernard, stated that "The Society's scope would encompass all the phenomena of plant as well as animal life", (ib. 1849 I, pp. I–XI). Biology was thus added to the sciences listed by Comte. Indeed, Rayer's patronage as well as his permanent and active support were a decisive help to Claude Bernard on his scientific road. (See John E. Lesch: *Science and Medicine in France. The Emergence of Experimental Physiology, 1790–1855*. Harvard University Press, 1984.)

Acknowledgments

The author is deeply indebted to Professor St. Wolf for translating the manuscript, to Miss Molitor, librarian at the section of History of Medicine at the Bibliothèque Universitaire, to Miss Chapuis, documentaliste at the Bibliothèque de l'Académie Nationale de Médecine and to Miss Mallet, secretary at Hôpital Tenon.

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Abbreviations for Libraries:

Acad Med: Académie Nationale de Médecine, 75272 Paris, C. 06., France

Bib. Fac. Méd., Bibliothéque Universitaire, 12 Rue de l'Ecole de Médecine, 75006 Paris, France

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